

**Pulmonary vein re-isolation as a routine strategy regardless of symptoms: the
PRESSURE randomized controlled trial**

Short title: Pulmonary vein re-isolation as a routine strategy

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ABSTRACT

Background:

Enduring pulmonary vein isolation (PVI) remains elusive. PV reconnection is strongly linked to arrhythmia recurrence.

Objectives:

We aimed to determine whether a strategy of early re-isolation of PV reconnection in all patients, irrespective of symptoms, would reduce AF recurrence and improve quality-of-life.

Methods:

80 patients with paroxysmal AF were randomized 1:1 following contact force-guided PVI to either Standard Care (SC) or to undergo repeat electrophysiology study after 2 months regardless of symptoms (Repeat Study (RS)). At the initial procedure, PVI was demonstrated by entrance/exit block and adenosine administration after ≥ 20 mins wait. At repeat study, all sites of PV reconnection were re-ablated. Patients recorded ECGs daily and whenever symptomatic for 12 months, using a handheld monitor. Recurrence was defined as ≥ 30 secs of atrial tachyarrhythmia (AT) after a 3-month blanking period. The AFEQT quality-of-life questionnaire was completed at baseline, 6 and 12 months.

Results:

All 40 RS group patients attended for repeat study after 62 ± 6 days, of whom 25 (62.5%) had reconnection of 41 (26%) PVs. There were no complications related to these procedures. Subjects recorded a total of 32,203 ECGs (380[335-447] per patient) during 12.6[12.2-13.2] months follow-up. AT recurrence was significantly lower for the RS group (17.5% vs. 42.5%, $P=0.03$), as was AT burden ($P=0.03$). AFEQT quality-of-life scores were higher in the RS group at 6 months ($P<0.001$) and 12 months ($P=0.02$).

Conclusion:

A strategy of routine repeat assessment with re-isolation of PV reconnection improves freedom from AT recurrence, AT burden and quality-of-life compared to current standard care.

5 **KEYWORDS:** Catheter ablation; atrial fibrillation; pulmonary vein isolation; pulmonary vein reconnection

CONDENSED ABSTRACT:

Late PV reconnection following PVI is common and is strongly associated with atrial tachyarrhythmia (AT) recurrence. Eighty patients with paroxysmal AF were randomized to
10 either Standard Care (SC) or to undergo repeat electrophysiology study and re-isolation of reconnected PVs after 2 months irrespective of symptoms (Repeat Study (RS)). All patients recorded ECGs daily and whenever symptomatic. Twenty-five (62.5%) RS group patients had PV reconnection. During 12 months' follow-up, AT recurrence (17.5% vs. 42.5%), AT burden and AFEQT quality-of-life scores at 6 and 12 months were significantly better in the
15 RS group compared to the SC group.

ABBREVIATIONS LIST:

AF - atrial fibrillation

AT - atrial tachyarrhythmia

PRESSURE - Pulmonary vein RE-isolation as a routine Strategy: a SUccess Rate Evaluation

5 PV - pulmonary vein

PVI - pulmonary vein isolation

RS - Repeat Study

SC - Standard Care

WACA - wide area circumferential ablation

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INTRODUCTION:

Since the pulmonary veins (PVs) were first identified as the primary sources of initiating triggers of paroxysmal atrial fibrillation (AF) (1), catheter ablation to achieve pulmonary vein isolation (PVI) has become the cornerstone of AF ablation (2). Even in more persistent forms of AF, additional atrial ablation does not improve outcomes over PVI alone (3,4). However, creating durable PVI is difficult to achieve, with contemporary studies demonstrating that up to two-thirds of patients after a successful PVI procedure have PV reconnection at protocol-mandated repeat electrophysiology study (5,6). PV reconnection is well-recognized as the leading cause of atrial tachyarrhythmia (AT) recurrence following PVI (7-10), which occurs in around 30-40% of patients after a single procedure (11-13). Such AT recurrences significantly impact upon quality-of-life (14,15).

Currently, patients re-presenting with AT recurrence commonly undergo repeat ablation, and this has been shown to increase success rates (8). However, there can be a significant delay between symptomatic recurrence and the second procedure, during which time quality-of-life can suffer. While clinical success rates have remained relatively static, the safety of AF ablation has improved significantly over recent years (16,17). Given the high rates of late PV reconnection still seen, we designed the Pulmonary vein RE-isolation as a routine Strategy: a SUccess Rate Evaluation (PRESSURE) study to test the hypothesis that a strategy of assessment and re-isolation of all PV reconnection two months after the initial AF ablation, irrespective of symptoms, would reduce AT recurrence and improve quality-of-life.

METHODS:

Patient population:

Consecutive patients were recruited from a single tertiary center in the UK. Study inclusion criteria were as follows: a current pattern of paroxysmal AF (defined as ECG-proven

episodes of AF which are self-limiting and last less than 7 days on each occasion, or which were cardioverted electrically or pharmacologically less than 48 hours from onset), aged over 18 years and scheduled for catheter ablation using radiofrequency energy. Exclusion criteria were: previous ablation procedure for AF, prosthetic mitral valve replacement, severe structural cardiac abnormality, infiltrative cardiomyopathy, severe left ventricular systolic dysfunction (ejection fraction <35%) and pregnancy. All patients provided written informed consent and the study was approved by the UK National Research Ethics Service and the Institutional Research Committee.

Patients were enrolled prior to their initial ablation but randomization was delayed until immediately after the procedure in order to avoid possible bias or influence on the ablation. Randomization was in a 1:1 ratio using a custom-written two- and four-block randomization program to either Standard Care (SC) or to undergo a repeat electrophysiology study after 2 months, irrespective of symptoms (Repeat Study (RS) group). Due to the nature of the study design, randomization was blinded to neither patient nor clinician but all study analyses were performed by blinded observers. A diagram defining study time-periods is shown in Figure 1.

Initial PVI procedure:

Patients taking amiodarone had this stopped a minimum of 2 months prior to their PVI procedure; if this was not possible, the patient was excluded. All other anti-arrhythmic drugs were stopped 5 days prior. Patients taking warfarin continued this peri-procedurally, with an INR level of 2.0-3.5 considered acceptable. Non-Vitamin K anticoagulants were stopped 24-48 hours pre-procedure.

PVI was performed under conscious sedation with fentanyl and midazolam or general anesthesia in a standard fashion. Vascular access was gained under direct ultrasound guidance, as is standard in our institution (18). A 3-dimensional navigation system (CARTO

3, Biosense Webster, Inc., Diamond Bar, CA) was used in all cases to create an electroanatomical map of the left atrium and, where possible, this was integrated with a computed tomography or magnetic resonance imaging reconstruction of the left atrium (CartoMerge, Biosense Webster, Inc.). PVI was performed in a wide area circumferential ablation (WACA) pattern using a 3.5mm irrigated tip contact force-sensing RF ablation catheter (Thermocool SmartTouch, Biosense Webster, Inc.). Power settings were 25-30W for the posterior wall and 30-35W for other regions. A contact force of 5-40g with application duration of 20-40s was targeted at each site, aiming for local signal attenuation of >80%. Automated lesion tagging (VisiTag, Biosense Webster, Inc.) was used to mark the location of each lesion, using standardized settings as follows: Catheter Position Stability - Minimum time 10sec, Maximum range 2mm; Force Over Time - Time 30%, Minimum force 5g; Lesion tag size - 2mm. Contiguous lesions around the WACA circle were aimed for. Cavotricuspid isthmus ablation was permitted in patients with documented typical right atrial flutter, but no additional left atrial ablation was performed and no attempt was made to look for extra-PV triggers. AF that persisted after PVI was terminated with electrical cardioversion.

Acute PVI was confirmed by demonstrating entry and exit block with a 20-pole circular mapping catheter (Lasso NAV Eco, Biosense Webster, Inc.) placed sequentially in each of the PVs. On-going PVI was confirmed a minimum of 20 minutes after isolation of that ipsilateral PV pair, with intravenous adenosine boluses (12-18mg) administered to unmask sites of dormant conduction. Further ablation was performed at sites of overt or unmasked reconnection to re-isolate the PVs.

Post-procedure anti-arrhythmic drug therapy:

Pre-procedure anti-arrhythmic medications, including beta-blockers and rate-limiting calcium channel-blockers were restarted post-procedure and stopped after 4 weeks. Subsequent re-

initiation of therapy was permitted by the attending physician to treat clinical arrhythmia recurrences, but was stopped again at the end of the 3-month blanking period.

Repeat Study group:

Repeat electrophysiology study was performed 2 months after the initial procedure in all
5 patients in the RS group. Any re-initiated antiarrhythmic medications were stopped again 5
days prior. The repeat study was performed using 3-dimensional mapping in the same way as
for the initial procedure. Each PV was assessed for reconnection using a 20-pole circular
catheter. All identified sites of reconnection were ablated to re-isolate the PVs. As for the
initial procedure, no additional left atrial ablation beyond PVI was performed. As pre-
10 specified, a data monitoring and safety committee review was held after half of the repeat
procedures in the RS group had been performed.

Standard Care group:

Patients in the SC arm did not undergo routine repeat electrophysiology study and, as per
international guidelines, repeat ablation was not performed within the first three months (2).
15 Management was otherwise identical to the RS group, with options of anti-arrhythmic drugs
or repeat ablation available as per standard clinical care for patients with symptomatic AT
after the 3-month blanking period.

ECG follow-up:

All patients were provided with a validated portable ECG monitor (Omron HCG-801-E,
20 Omron Healthcare, Kyoto, Japan) (19), and, having been trained in its use, were instructed to
self-record a 30-second ECG every day and additionally whenever they experienced
symptoms. ECG recordings were downloaded at each follow-up visit and were analyzed for
the presence and dates of any AT by experienced clinicians (YS, SG) blinded to treatment
allocation.

Patient follow-up:

Follow-up visits were arranged after 6 weeks and 3, 6 and 12 months. Any anti-arrhythmic medications restarted for symptomatic documented AT during the blanking period were stopped again 3 months post-initial ablation. The validated AFEQT quality-of-life

- 5 questionnaire, which involves 20 questions across 3 domains (symptoms, daily activities and treatment concerns) using a 7-point Likert scale, was completed at baseline and at 6 and 12 months (20).

Study outcomes:

- The primary outcome measure was AT recurrence occurring after a 3-month blanking period
10 following the initial ablation procedure. As per current guidelines, AT recurrence was defined as documented AF, atrial flutter or atrial tachycardia lasting ≥ 30 seconds (2,21).

Pre-specified secondary outcome measures were: quality-of-life 6 and 12 months after initial ablation; time to first AT recurrence; AT burden during the primary outcome period; re-initiation of anti-arrhythmic medication; and comparison of major complication rates.

- 15 Procedure-related complications consisted of cardiac tamponade, stroke/transient ischemic attack, myocardial infarction, severe PV stenosis, phrenic nerve paralysis, esophageal perforation or atrio-esophageal fistula, major vascular complications, and death. Definitions were as per international guidelines (2).

Sample size:

- 20 A formal sample size calculation was performed assuming a twelve month single-procedure success rate of 64% in the SC group, based on the ThermoCool AF trial results (22), and 90% in the RS group. Although difficult to predict due to the novel trial design, the estimated success rate in the RS group was based on the A4 study, in which up to two additional procedures were allowed within a 90-day blanking period for patients with early recurrence,

resulting in 89% freedom from AF at 12 months after a mean of 1.8 ± 0.8 procedures (23).

Using an alpha error of 0.05 and a beta of 20% (80% power), the number of patients required was 76 (38 in each group). Allowing for 5% attrition gave a total sample size of 80. The study was intentionally underpowered to detect a difference between groups of <25% as it was felt that the magnitude of the additional intervention required a clear and considerable reduction in AT recurrence to be considered acceptable in clinical practice.

Statistical analysis:

All endpoints were examined by means of an intention-to-treat analysis. Categorical variables and endpoints (including the primary endpoint) were summarized as counts (percentages) and compared with χ^2 or Fisher's exact test as appropriate. Continuous variables were checked for normality by visual inspection of the relevant histogram. Where normality was an unreasonable assumption, transformations of the data were attempted (e.g. log and exponential). Continuous variables that were normally distributed were expressed as means (\pm standard deviation) and were compared using Student's t-tests. Variables that were not normally distributed despite transformation were expressed as medians (interquartile range) and were compared using Mann-Whitney U tests. Time to first AT recurrence was assessed via Cox's Proportional Hazard model, and a comparison was made between groups using the log-rank test. All tests were two-sided and a *P*-value <0.05 was considered statistically significant.

RESULTS:

Study participants:

A CONSORT diagram showing recruitment to the study is shown in Figure 2. Patient demographics for the 80 subjects randomized in the study are provided in Table 1. The median CHADS-VASc score was higher in the SC group, though this will have been

influenced in part by the higher proportion of females in this group. There were no other statistically significant differences between groups at baseline.

Initial procedural characteristics:

There were no significant differences in procedural characteristics between groups (Table 2).

- 5 In 2 patients, the right inferior PV could not be safely isolated at the posterior aspect due to esophageal temperature rise, giving an overall PVI rate of 99.4%. Of the remaining PVs, acute reconnection (spontaneous or adenosine-mediated) was identified in 56 (17.6%) PVs in 38 (47.5%) patients. There was no difference in acute reconnection rates between groups (SC: 32 (20%) PVs in 18 (45%) patients; RS: 24 (15%) PVs in 20 (50%) patients; $P=0.30$ and $P=0.82$ respectively). All identified sites of acute reconnection were successfully ablated.

Repeat study procedural characteristics:

- All 40 patients randomized to the RS group had the repeat study performed, at a mean interval of 62 ± 6 days after the initial ablation. Thirty-eight patients were in sinus rhythm at the start of the repeat procedure, with 1 in AF and 1 in atrial flutter. The repeat study procedure duration was 80 [61-109] minutes, and fluoroscopy time and dose were 8.3 [6.8-12.0] minutes and 918 [498-1756] cGy/m² respectively. The 2 patients in whom the right inferior PV could not be isolated at the initial procedure were both subsequently randomized to the RS group. Including these 2 patients, late PV reconnection was identified in 25 (62.5%) patients, affecting 41 (26%) PVs. The distribution of reconnected PVs was as follows: left superior 6, left inferior 14, right superior 8 and right inferior 13. All these PVs were successfully re-isolated, including the 2 right inferior PVs not isolated at the initial procedure as the position of the esophagus was found to have changed at the repeat study. The median ablation time for re-isolation in these 25 patients was 5.1 [3.6–9.6] minutes.

In the SC group, 9 (22.5%) patients subsequently underwent a redo procedure for symptomatic arrhythmia recurrence after a median interval of 210 [173-233] days from the initial PVI. One of these redo procedures was performed in a patient with frequent symptomatic bursts of atrial ectopy but no sustained arrhythmia ≥ 30 s recorded on ECG, who was therefore categorized as not having experienced the primary endpoint. Eight patients were in sinus rhythm at the start of the procedure, with 1 in an atypical atrial flutter. Eight (89%) of these 9 patients had PV reconnection, affecting 18 (50%) PVs. The median procedure and ablation times were 115 [76-170] minutes and 12.3 [6.9-15.6] minutes respectively, and the fluoroscopy time and dose were 9.9 [6.0-14.8] minutes and 1024 [254-1709] cGy/m².

No patient in either group underwent a third left atrial ablation procedure during follow-up.

Patient follow-up:

Patients were followed-up clinically for 382 [372-402] days (12.6 [12.2-13.2] months), with no difference in follow-up duration between groups. ECG follow-up, defined as the number of days from initial ablation to the date of the last self-recorded ECG was 380 [367-400] days, and also did not differ between groups (Table 2).

Patients recorded a total of 32,203 ECGs (380 [335-447] per patient) during follow-up. Of these, 22,789 ECGs were recorded during the primary outcome period, with no difference between groups (SC: 278 [222-326] vs. RS: 274 [242-315] per patient, $P=0.81$).

Primary Endpoint

Over 1 year of follow-up, significantly fewer patients in the RS group (7 (17.5%)) experienced the primary endpoint compared to the SC group (17 (42.5%), $P=0.03$). As detailed above, 8 of these 17 SC group patients underwent a redo procedure, with the

remainder opting to continue with medical management due to either low symptom burden or adequate symptom control with previously-ineffective antiarrhythmic medication. One (12.5%) of these 8 patients had further AT recurrence during remaining follow-up (5.6 [4.5-6.6] months). In the RS group, 3 (12%) of the 25 patients with PV reconnection at repeat study had AT recurrence compared to 4 (27%) of those without.

Time to first recurrence

Figure 3 shows Kaplan-Meier curves for the 2 groups, with the final follow-up date taken as the date of the last self-recorded ECG for censored cases. The log-rank test was statistically significant ($P=0.02$). Including a time-dependent covariate for randomized group

demonstrated that the proportional hazards assumption required for the Cox proportional hazards model was valid (P -value for interaction term 0.78). The Cox model including only randomized group led to a hazard ratio of 0.35 (95% confidence interval 0.15-0.86, $P=0.02$).

CHADS-VASc score and left atrial diameter were assessed as co-variants of potential clinical interest. Using forward and backward selection methods, via Akaike's Information Criteria (24), led to a model which only included randomized group (which was forced into the model). Patients in the RS group were 64% less likely to have a recurrence than those in the SC group (Hazard ratio 0.36, 95% confidence interval 0.15-0.88, $P=0.02$).

Kaplan Meier curves for the 2 groups including clinical redo procedures for documented AT in SC group patients are shown in Figure 4. The log-rank P value was no longer significant.

AT burden during the primary outcome period:

Total group AT burden, defined as the number of patient-days on which AT was documented during the primary outcome period, was markedly lower in the RS than the SC group (91 vs.

127 days), and the median number of days per patient was significantly lower (RS: 0 [0–0] vs. SC: 0 [0–3], $P=0.03$).

Procedure-related adverse events:

No patient suffered death or stroke during the study. One patient developed cardiac

5 tamponade during the initial procedure; this was successfully drained percutaneously without clinical sequelae. This patient was withdrawn from the study prior to randomization but this complication is included in the overall rate. A further patient developed right phrenic nerve palsy following the initial PVI. This resolved completely during the follow-up period. The overall serious complication rate associated with 81 initial procedures was 2.5%.

10 None of the 40 repeat procedures in the RC group were associated with any adverse event. One patient in the SC group who underwent repeat ablation for clinical recurrence suffered a post-procedural transient ischemic attack (possibly related to non-absorption of her oral anticoagulant due to vomiting). Considering all procedures, the overall serious complication rates for the two groups were not different (RS: 1 in 40 patients (2.5%) in 80
15 procedures (1.25%) vs. SC: 1 in 40 patients (2.5%) in 49 procedures (2.0%), $P>0.99$ for both).

AFEQT quality-of-life scores:

Baseline AFEQT scores were not different between groups (RS: 46.3 [36.1-69.1] vs. SC: 47.7 [30.1-73.3], $P=0.90$). At six months after the initial PVI procedure, AFEQT scores were
20 significantly higher in the RS group than the SC group (88.0 [79.6-96.3] vs. 65.7 [49.5-82.9], $P<0.001$), and this was maintained at twelve months (91.9 [79.5-99.1] vs. 77.3 [67.6-94.5], $P=0.02$).

AT-related urgent hospital admissions:

Excluding elective admissions for repeat AF ablation in both groups, patients in the SC group had markedly more urgent admissions to hospital relating to AT, either as emergency presentations or for electrical cardioversion (11 vs. 3), with a trend towards significance ($P=0.10$).

5 **Re-initiation of medication:**

Significantly fewer patients in the RS group had anti-arrhythmic medication, including beta-blockers and calcium-channel blockers, re-initiated in the primary outcome period for symptomatic clinical recurrence (either on a regular or “pill-in-the-pocket” basis) than in the SC group (4/40 (10%) vs. 13/40 (32.5%), $P=0.03$).

10 **Early recurrence of AT:**

A planned post-hoc analysis of the relationship between early recurrence of AT and the primary endpoint was performed. As shown in Figure 1, the first 4 weeks post-ablation was regarded as an absolute blanking period based on previous published data suggesting this to be more reflective of the “true” blanking period (25). The early recurrence period was pre-
15 specified as the period from 4 weeks to the repeat study date (RS group) or end of the blanking period (SC group).

In the SC group, 14 patients had early recurrence, of whom 12 (86%) went on to experience the primary endpoint. This proportion was significantly reduced in the RS group (5 (38%) of 13 with early recurrence, $P=0.02$). Comparatively, for those without early
20 recurrence (either no recurrence or recurrence confined only to the first 4 weeks), the risk of reaching the primary endpoint was low (7/53 (13%)), and the difference between groups did not reach significance (SC: 5/26 (19%) vs. RS: 2/27 (7%), $P=0.25$). The addition of early recurrence to the multivariable model was significant, with patients experiencing early recurrence beyond 4 weeks being nearly 10 times more likely to reach the primary endpoint

than those without early recurrence (Hazard ratio 9.75, 95% confidence interval 3.94-24.15, $P<0.001$). The addition of early recurrence also increased the significance of the randomized group ($P=0.005$).

DISCUSSION:

5 Main findings:

In this randomized controlled trial, we found that a strategy of re-assessment and ablation of PV reconnection after 2 months, irrespective of symptoms, reduces AT recurrence and burden and improves quality-of-life when compared to current standard care, where repeat procedures are only performed for arrhythmia recurrence after an initial blanking period.

10 While previous data have suggested the potential benefit of early re-intervention in symptomatic patients (26), to our knowledge, this is the first study to randomize patients irrespective of symptoms to PV re-assessment and re-intervention.

Freedom from AT:

Our study utilized intensive ECG monitoring, which is recognized to result in higher AT
15 detection rates (27), and stringent arrhythmia duration criteria of ≥ 30 seconds as per international guidelines for clinical trials (2). AT recurrence occurred in 42.5% of patients in the SC group, in keeping with single-procedure success rates in other contemporary studies (12,13). Comparatively, routine early re-intervention resulted in a success rate of 82.5% with the same degree of intensive monitoring. Previous work that has shown that 10-25% of
20 patients may have non-PV triggers (1,28,29), and we did not attempt to look for or ablate these. It is also possible that further PV reconnection following re-ablation may have contributed to recurrence in some cases. Nevertheless, early re-intervention conferred a highly significant absolute improvement in freedom from AT of 25%.

After including clinical redo procedures performed for documented AT recurrence in SC group patients, there was no longer a significant difference in freedom from AT between groups. However, the study was not powered to detect such a difference and, furthermore, follow-up was very short for those patients who underwent a clinical redo procedure, introducing a discrepancy between follow-up periods for the 2 groups. Perhaps more importantly, definitive treatment (the redo procedure) was significantly delayed in these patients compared to the Repeat Study group (210 vs. 62 days), resulting in more AT burden (with more consequent hospital admissions and cardioversions) and more re-initiation of medication in the intervening period. These factors are likely to explain the significant differences in quality-of-life between groups.

As previous histological studies in animal models have shown that ablation lesion maturation is complete within 1 week after delivery (30,31), it does not seem likely that there is a significant mechanistic difference between reintervention after 2 months and reintervention at a later stage. It would therefore seem that improvements in outcomes are primarily due to a difference in timing of reintervention, which pre-empts later recurrence.

Context of our results:

PVI remains the cornerstone of successful AF ablation, with recent studies demonstrating a lack of benefit from additional left atrial ablation even in persistent AF (3,4). However, this study and others have shown how infrequently that is achieved with a single procedure (5,6). A very recent study attempting to improve durability of PVI by targeting a high Force-Time Integral value still showed a significant rate of late reconnection and additionally reported an increased complication rate (32).

The relationship between PV reconnection and AF recurrence has been clearly established (7-10), and while it has previously been shown that complete durable PVI is not

essential in all cases to prevent AT recurrence (33), nevertheless, the aim for operators at the initial procedure is to deliver exactly this. Furthermore, if a patient's AF is truly PV trigger-driven, the only way to achieve certainty that it will not recur is through complete durable PVI. Additional intervention to make up for the limitations of the initial procedure is therefore a potentially logical adjunct.

Implications for clinical practice:

Ideally, it would be possible to identify those patients with PV reconnection to focus re-intervention towards those with most to gain from it but, at present, imaging modalities cannot accurately identify PV reconnection (34). We have therefore tested a strategy of invasive re-assessment for PV reconnection in all patients and, while this has resulted in a clear overall improvement in outcomes, there would be significant health economic implications if this were to be adopted into clinical practice. However, the greatest benefit appears to have been in the sub-set of patients with early AT recurrence beyond 4 weeks within the conventional blanking period. We have previously reported that early recurrence in this time period is strongly associated with PV reconnection (35), and this and other studies have demonstrated the relationship between such recurrence and post-blanking AT recurrence (25,36). Although there were no serious complications associated with elective repeat procedures in this study, we acknowledge that this is a relatively small sample size to detect these, and procedures were undertaken by experienced operators in a high-volume center. It may therefore be that targeting patients with such early recurrence may provide the optimal risk/benefit balance and cost-effectiveness.

LIMITATIONS:

The study has some important limitations. Firstly, the size of the study is small, having been powered to detect only a large absolute difference between groups. This was done

deliberately as it was felt that the potential additional risk associated with a routine repeat procedure strategy could only be justified by a major improvement in success rates. However, whilst none of the repeat studies were associated with a complication, the size of this study means our ability to detect rare complications is limited. Secondly, this study assessed point-by-point ablation with radiofrequency energy performed by experienced operators. Its role in patients receiving alternate energy sources such as cryoablation cannot be assumed and it is not possible to say with certainty whether our results would be replicated if performed by less experienced physicians. Thirdly, we used validated hand-held monitors to document AF recurrence, believing these provided the most comprehensive non-invasive rhythm monitoring option. Although patients were asked to provide recordings every day and whenever symptomatic, it is possible that asymptomatic episodes lasting less than 24 hours may have been missed. Furthermore, follow-up was relatively short at 12 months. Finally, it was not possible to blind patients to treatment allocation due to the nature of the study, which could have influenced quality-of-life scores.

CONCLUSIONS:

A strategy of routine repeat electrophysiology study to assess for and treat PV reconnection in patients with paroxysmal AF provides significant improvements in freedom from AT recurrence, AT burden, and quality-of-life compared to current standard care. Particular benefit from this strategy was seen in those with early AT recurrence beyond 4 weeks within the conventional blanking period.

PERSPECTIVES:

Competency in Medical Knowledge: In patients with paroxysmal atrial fibrillation undergoing radiofrequency catheter ablation, routine repeat electrophysiology study after two months to assess for and treat pulmonary vein reconnection provides significant improvements in freedom from atrial tachyarrhythmia recurrence, atrial tachyarrhythmia burden and quality-of-life compared to current standard care.

Competency in Patient Care: Patients undergoing radiofrequency catheter ablation for paroxysmal atrial fibrillation should be made aware that there is only an approximately 40% likelihood that all pulmonary veins will remain isolated following the procedure. They should be informed that early re-intervention may be beneficial, especially if they experience early recurrence of atrial tachyarrhythmia beyond four weeks after the initial procedure.

Translational Outlook 1: As this was a relatively small, single-center study, a larger multicenter study should be undertaken to assess the safety of a strategy of routine re-intervention in all patients.

Translational Outlook 2: Particular benefit from routine re-intervention to assess for and treat pulmonary vein reconnection was seen in those patients with early recurrence of atrial tachyarrhythmia in the blanking period beyond four weeks after the initial procedure. Further study of focusing this strategy on these individuals should be undertaken.

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REFERENCES

- (1) Haissaguerre M, Jais P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; 339:659-666.
- (2) Calkins H, Kuck KH, Cappato R et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Heart Rhythm* 2012; 9:632-696.
- (3) Verma A, Jiang CY, Betts TR et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015; 372:1812-1822.
- (4) Wynn GJ, Panikker S, Morgan M et al. Batrial linear ablation in sustained nonpermanent AF: Results of the substrate modification with ablation and antiarrhythmic drugs in nonpermanent atrial fibrillation (SMAN-PAF) trial. *Heart Rhythm* 2016; 13:399-406.
- (5) Neuzil P, Reddy VY, Kautzner J et al. Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study. *Circ Arrhythm Electrophysiol* 2013; 6:327-333.
- (6) Kuck KH, Hoffmann BA, Ernst S et al. Impact of Complete Versus Incomplete Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 Trial. *Circ Arrhythm Electrophysiol* 2016; 9:e003337.
- (7) Verma A, Kilicaslan F, Pisano E et al. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation* 2005; 112:627-635.

- (8) Callans DJ, Gerstenfeld EP, Dixit S et al. Efficacy of repeat pulmonary vein isolation procedures in patients with recurrent atrial fibrillation. *J Cardiovasc Electrophysiol* 2004; 15:1050-1055.
- (9) Nanthakumar K, Plumb VJ, Epstein AE, Veenhuyzen GD, Link D, Kay GN.
5 Resumption of electrical conduction in previously isolated pulmonary veins: rationale for a different strategy? *Circulation* 2004; 109:1226-1229.
- (10) Ouyang F, Antz M, Ernst S et al. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. *Circulation* 2005;
10 111:127-135.
- (11) Macle L, Khairy P, Weerasooriya R et al. Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial. *Lancet* 2015; 386:672-679.
- (12) Ghanbari H, Jani R, Hussain-Amin A et al. Role of adenosine after antral pulmonary
15 vein isolation of paroxysmal atrial fibrillation: A randomized controlled trial. *Heart Rhythm* 2016; 13:407-415.
- (13) Kuck KH, Brugada J, Furnkranz A et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med* 2016; 374:2235-2245.
- (14) Reynolds MR, Walczak J, White SA, Cohen DJ, Wilber DJ. Improvements in
20 symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes* 2010; 3:615-623.

- (15) Wokhlu A, Monahan KH, Hodge DO et al. Long-term quality of life after ablation of atrial fibrillation the impact of recurrence, symptom relief, and placebo effect. *J Am Coll Cardiol* 2010; 55:2308-2316.
- 5 (16) Cappato R, Calkins H, Chen SA et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation* 2005; 111:1100-1105.
- (17) Cappato R, Calkins H, Chen SA et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; 3:32-38.
- 10 (18) Wynn GJ, Haq I, Hung J et al. Improving safety in catheter ablation for atrial fibrillation: a prospective study of the use of ultrasound to guide vascular access. *J Cardiovasc Electrophysiol* 2014; 25:680-685.
- (19) Kaleschke G, Hoffmann B, Drewitz I et al. Prospective, multicentre validation of a simple, patient-operated electrocardiographic system for the detection of arrhythmias and electrocardiographic changes. *Europace* 2009; 11:1362-1368.
- 15 (20) Spertus J, Dorian P, Bubien R et al. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011; 4:15-25.
- (21) Kirchhof P, Auricchio A, Bax J et al. Outcome parameters for trials in atrial fibrillation: executive summary. *Eur Heart J* 2007; 28:2803-2817.
- 20 (22) Wilber DJ, Pappone C, Neuzil P et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010; 303:333-340.

- (23) Jais P, Cauchemez B, Macle L et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008; 118:2498-2505.
- (24) Akaike H. A new look at the statistical model identification. *IEEE Transactions on Automatic Control* 1974; 19:716-723.
- 5 (25) Themistoclakis S, Schweikert RA, Saliba WI et al. Clinical predictors and relationship between early and late atrial tachyarrhythmias after pulmonary vein antrum isolation. *Heart Rhythm* 2008; 5:679-685.
- (26) Lellouche N, Jais P, Nault I et al. Early recurrences after atrial fibrillation ablation: prognostic value and effect of early reablation. *J Cardiovasc Electrophysiol* 2008; 19:599-605.
- 10 (27) Charitos EI, Ziegler PD, Stierle U et al. How often should we monitor for reliable detection of atrial fibrillation recurrence? Efficiency considerations and implications for study design. *PLoS One* 2014; 9:e89022.
- (28) Lin WS, Tai CT, Hsieh MH et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. *Circulation* 2003; 107:3176-3183.
- 15 (29) Zhao Y, Di BL, Trivedi C et al. Importance of non-pulmonary vein triggers ablation to achieve long-term freedom from paroxysmal atrial fibrillation in patients with low ejection fraction. *Heart Rhythm* 2016; 13:141-149.
- (30) Huang SK, Graham AR, Wharton K. Radiofrequency catheter ablation of the left and right ventricles: anatomic and electrophysiologic observations. *Pacing Clin Electrophysiol* 1988; 11:449-459.
- 20 (31) Wittkampf FH, Hauer RN, Robles de Medina EO. Control of radiofrequency lesion size by power regulation. *Circulation* 1989; 80:962-968.

- (32) Kautzner J, Neuzil P, Lambert H et al. EFFICAS II: optimization of catheter contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation. *Europace* 2015; 17:1229-1235.
- 5 (33) Pratola C, Baldo E, Notarstefano P, Toselli T, Ferrari R. Radiofrequency ablation of atrial fibrillation: is the persistence of all intraprocedural targets necessary for long-term maintenance of sinus rhythm? *Circulation* 2008; 117:136-143.
- (34) Harrison JL, Sohns C, Linton NW et al. Repeat left atrial catheter ablation: cardiac magnetic resonance prediction of endocardial voltage and gaps in ablation lesion sets. *Circ Arrhythm Electrophysiol* 2015; 8:270-278.
- 10 (35) Das M, Wynn GJ, Morgan M et al. Recurrence of atrial tachyarrhythmia during the second month of the blanking period is associated with more extensive pulmonary vein reconnection at repeat electrophysiology study. *Circ Arrhythm Electrophysiol* 2015; 8:846-852.
- 15 (36) Liang JJ, Elafros MA, Chik WW et al. Early recurrence of atrial arrhythmias following pulmonary vein antral isolation: Timing and frequency of early recurrences predicts long-term ablation success. *Heart Rhythm* 2015; 12:2461-2468.

FIGURE LEGENDS:

Figure 1: PRESSURE Study timeline

Graphical representation of blanking and recurrence periods during the study. For both randomization groups, the clinical blanking period (during which recurrence did not

- 5 contribute to the primary endpoint) was 3 months from the date of the initial ablation. For the purposes of a pre-specified sub-analysis, the first 4 weeks after the initial PVI procedure was categorized as an absolute blanking period, with episodes of AT occurring from this point until 3 months (SC group) or the repeat PVI (RS group) being considered as early recurrence of AT (ERAT).

10 *Figure 2: PRESSURE Study CONSORT diagram*

Screening, enrolment, randomization and follow-up of all randomized patients.

“Amiodarone” under ineligibility criteria denotes a patient whose ablation procedure was scheduled too soon after screening to allow the protocol-mandated 2 month amiodarone withdrawal period.

15 *Figure 3: Atrial tachyarrhythmia-free survival*

Kaplan–Meier estimates of freedom from documented AT after an initial 3-month blanking period.

Figure 4: Atrial tachyarrhythmia-free survival including clinical redo procedures in the SC group

- 20 Kaplan–Meier estimates of freedom from documented AT including clinical redo procedures in the SC group and a 3-month blanking period following the index procedure.

Table 1: Baseline Patient Characteristics

	All patients (n=80)	Standard Care (n=40)	Repeat Study (n=40)	<i>P</i>
Age, years	61.5 [55.8-68.0]	63.1 [57.8-68.2]	58.5 [53.0-66.2]	0.07
Male gender	42 (53%)	18 (45%)	24 (60%)	0.26
LA diameter (AP), mm	38.5±5.8	38.2±6.5	38.8±5.2	0.63
LV ejection fraction >55%	78 (98%)	39 (98%)	39 (98%)	>0.99
Hypertension	36 (45%)	22 (55%)	14 (35%)	0.12
Ischemic heart disease	6 (8%)	4 (10%)	2 (5%)	0.68
Obstructive sleep apnea	4 (5%)	1 (3%)	3 (8%)	0.62
Prior stroke	3 (4%)	2 (5%)	1 (3%)	>0.99
Diabetes mellitus	3 (4%)	3 (8%)	0 (0%)	0.24
CHA ₂ DS ₂ -VASc score	1 [1-3]	2 [1-3]	1 [0-2]	0.01
Anti-arrhythmic drugs	48 (60%)	26 (65%)	22 (55%)	0.49
Flecainide	36 (45%)	18 (45%)	18 (45%)	
Sotalol	11 (14%)	8 (20%)	3 (8%)	
Dronedarone	1 (1%)	0 (0%)	1 (3%)	
Beta-blockers	54 (68%)	26 (65%)	28 (70%)	0.81
Calcium channel blockers	5 (6%)	3 (8%)	2 (5%)	>0.99
ACE-I/ARB	23 (29%)	12 (30%)	11 (28%)	>0.99
Anticoagulation	53 (66%)	31 (78%)	22 (55%)	0.06
Warfarin	39 (49%)	26 (65%)	13 (33%)	
NOAC	14(18%)	5(13%)	9(23%)	

Table 1: Baseline characteristics of all study participants and by randomization group.

AP - anteroposterior; ACE-I - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; NOAC - non-Vitamin K oral anticoagulant

Table 2: Procedural and Follow-up Details

	All patients (n=80)	Standard Care (n=40)	Repeat Study (n=40)	P
Initial procedural details				
Procedure duration, mins	165.4±38.2	166.4±38.2	164.4±38.2	0.81
Total ablation time, mins	43.9±11.5	44.3±11.5	43.5±11.5	0.72
General anesthesia	60 (75%)	29 (73%)	31 (78%)	0.80
Rhythm at start of procedure				0.52
Sinus rhythm	69 (86%)	36 (90%)	33 (82%)	
AF	11 (14%)	4 (10%)	7 (18%)	
Cavotricuspid isthmus ablation	6 (8%)	3 (8%)	3 (8%)	>0.99
Radiation dose, cGy/m ²	1155 [732-1510]	1158 [726-1441]	1153 [733-1624]	0.71
Follow-up details				
Follow-up duration to last clinical review, days	382 [372-402]	382 [271-402]	382 [374-402]	0.86
Follow-up duration to last self-recorded ECG, days	380 [367-399]	379 [366-401]	380 [373-399]	0.60
Total ECG recordings	380 [336-446]	372 [334-439]	383 [340-447]	0.86
ECG recordings in primary outcome period	276 [231-318]	278 [222-326]	274 [242-315]	0.81
Anti-arrhythmic drugs continued in initial 4 weeks	43 (54%)	23 (58%)	20 (50%)	0.65
Additional anti-arrhythmic drugs in blanking period	19 (24%)	10 (25%)	9 (23%)	>0.99

Table 2: Procedural and follow-up details for all study participants and by randomization group.